

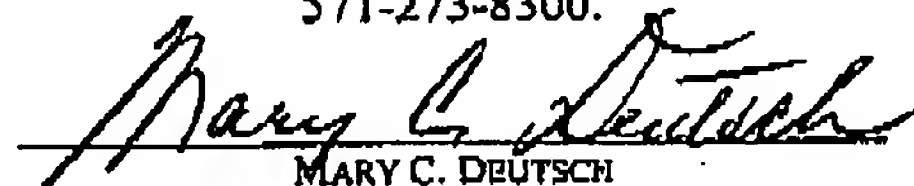
## PATENT

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: CHRISTOPHER JOHN LAWSON	Examiner: Unknown	<del>RECEIVED</del> CENTRAL FAX CENTER
Serial No.: 10/563,745	Group Art Unit: 1616	JUL 31 2007
Filed: August 29, 2006	Docket No. VOS0049/US	
For: STEROID MODIFIED SOLATRIOSES	By facsimile: 8 pgs	

Mail Stop EBC  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

HEREBY CERTIFY THAT ON JULY 31, 2007, THIS  
CORRESPONDENCE IS BEING FACSIMILE TRANSMITTED TO  
THE UNITED STATES PATENT AND TRADEMARK OFFICE  
TO GROUP ART UNIT #1616 AT FAX NUMBER  
571-273-8300.

  
MARY C. DEUTSCH

**REQUEST FOR CORRECTED PUBLICATION UNDER 37 CFR 1.221(b)**

Dear Sir or Madam:

It is respectfully requested that a Corrected Publication be issued in connection with the subject patent application in accordance with the provisions of 37 CFR 1.221(b), as follows:

- (A) This request is filed within two months of the date of patent publication; and
- (B) The publication contains a material mistake made by the US Patent Office in claims 8, 9 and 10 by incorrectly identifying the scope of the claim by stating that "R<sup>5</sup> represents a straight or branched C<sub>1-4</sub> alkyl group," rather than the correct scope of --R<sup>5</sup> represents a straight or branched C<sub>1-14</sub> alkyl group.-- The specification also contains errors that contribute to the material error of the claims by presenting further error in the definition of the R<sup>5</sup> substituent. See paragraph [0018].

The mistakes in the claims are material, because the errors occur in the claims and affect the ability of the public to determine the scope of the provisional rights that applicant may seek to enforce upon issue of the patent.

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Page 2

In support of this Request, please find attached


- i) a marked up copy of the relevant pages of the publication (Attachment A);  
and
- ii) indication of where in the specification as filed the relevant text  
corresponding to errors (both material as listed above and non-material) to be  
corrected by Corrected Publication (Attachments B and C).

It is noted that the claims of the publication were properly taken from a preliminary amendment filed on January 6, 2006, but the published claims are in error with respect to the claims of the preliminary amendment.

Because the listed errors first occurred in the printed publication, and thus are not due to Applicant's mistake, no fee is required in connection with this Request for Corrected Publication. However, if any fees are found to be required, please charge the fees to deposit Account No. 50-1775.

Respectfully Submitted,

Dated: July 31, 2007

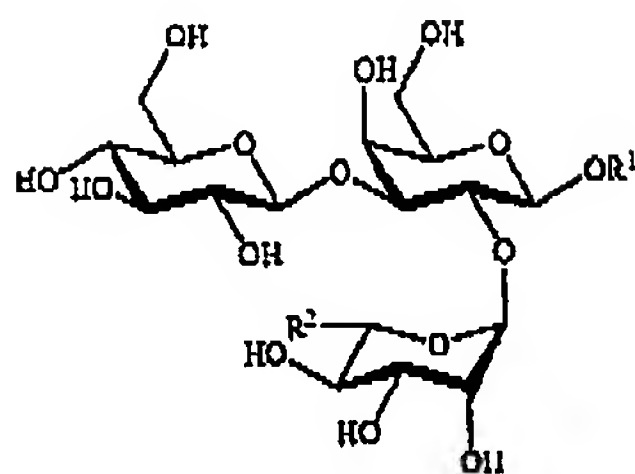
By:   
Dale A. Bjorkman, Reg. No. 33,084  
Customer No. 33,072  
Phone: 651-275-9811  
Facsimile: 651-351-2954

## ATTACHMENT A

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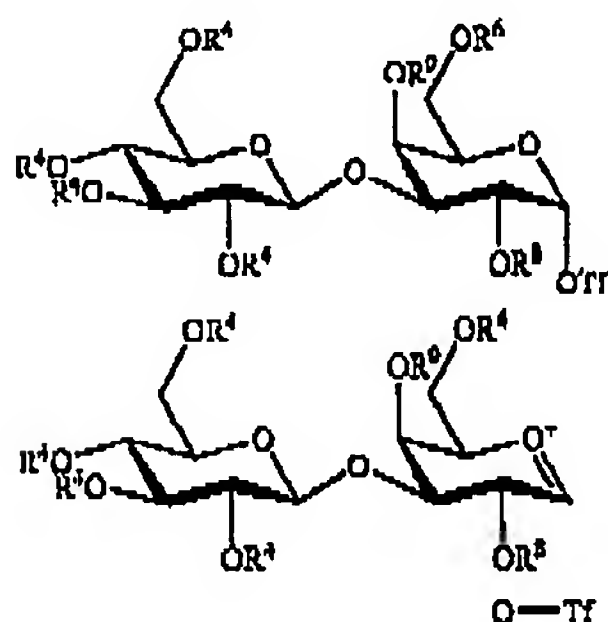
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Formula (I)

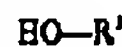
wherein  $R^1$  represents a steroid or a derivative thereof having a hydroxyl group in 3-position and no further unprotected hydroxyl groups; and  $R^2$  represents a straight or branched  $C_{1-4}$  alkyl group or a hydroxyl group.

[0011] The method of the present invention comprises the step of: reacting a compound of general formula (XIII):



Formula (XIII)

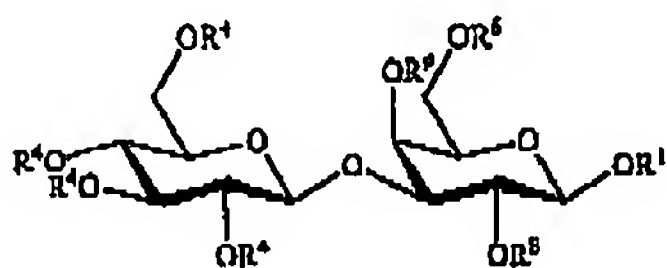
wherein each  $R^4$  independently represents a benzoyl, acetyl or pivoyl protecting group;  $R^5$  represents a pivoyl protecting group;  $R^6$  represents a chloroacetyl protecting group;  $R^7$  represents a benzoyl, acetyl or pivoyl protecting group and Tf represents a triflate leaving group; with a compound of general formula (XIV):



Formula (XIV)

wherein  $R^1$  is as defined above,

[0012] to yield a compound of general formula (XV):



Formula (XV)

wherein  $R^1$ ,  $R^4$ ,  $R^5$  and  $R^6$  are as defined above.

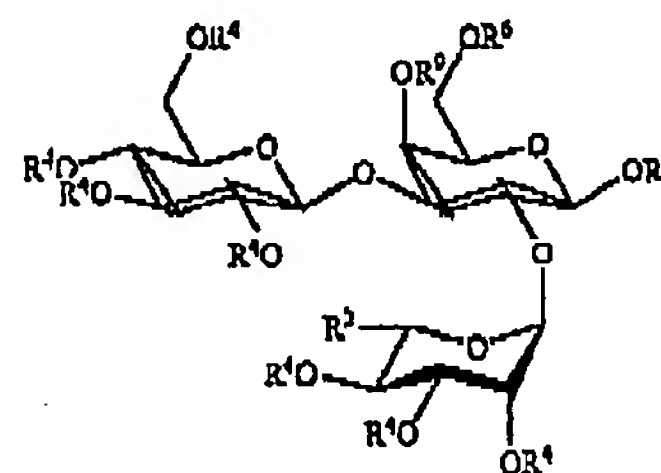
[0013] The compound of the above general formula (XV) may be transformed to the desired steroid modified solatriose:

ose of general formula (I) by any suitable method known in the art. A particular preferred procedure is described in detail below.

[0014] Furthermore, the present application provides steroid modified solatriose compounds of general formula (I) as defined above, wherein  $R^1$  represents a romatidin-3-yl, demissidin-3-yl, solanidin-3-yl or solasodin-3-yl group.

[0015] A further object of the present application is the provision of intermediate compounds useful for the synthesis of the steroid modified solatriose of general formula (I) defined above, namely:

[0016] A compound of general formula (XVII):

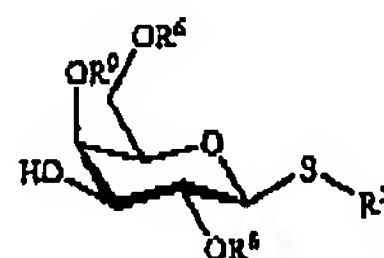


Formula (XVII)

wherein  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^5$  and  $R^6$  are as defined above.

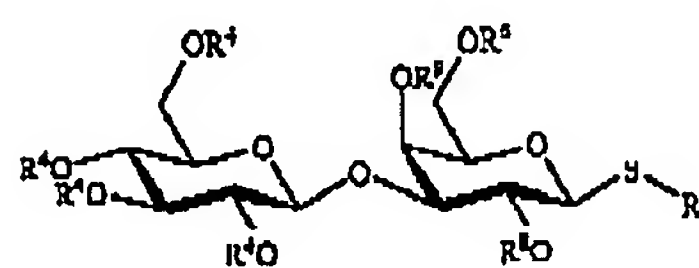
[0017] A compound of general formula (XV) as defined above

[0018] A compound of general formula (X):



Formula (X)

wherein  $R^4$ ,  $R^5$  and  $R^6$  are as defined above; and  $R^3$  represents a straight or branched  $C_{1-14}$  alkyl group or a phenyl group optionally substituted with one or more  $C_{1-4}$  alkyl groups, halogen atom such as Cl, F, Br or I, or  $NO_2$  group. A compound of general formula (XII):



Formula (XII)

wherein  $R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  are as defined above.

[0019] Further embodiments of the present application are described in the dependent claims.

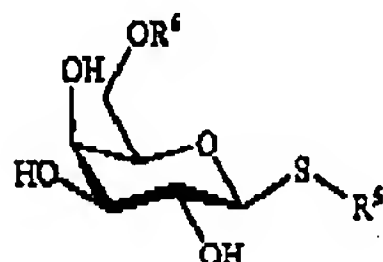
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[0030] Subsequently, the OH group in 6-position is selectively protected in step (D) using a bulky protecting group to yield a compound of general formula (VI)

Formula (VI)

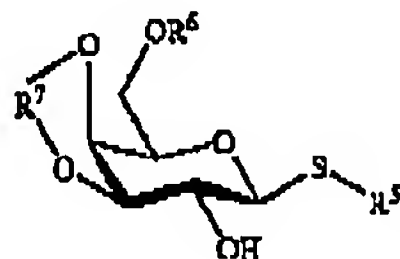


wherein  $R^5$  is as defined above; and  $R^6$  is a pivoyl, benzoyl or substituted benzoyl protecting group, whereby the substituents are selected from alkyl groups such as methyl, halogen atoms such as Cl, Br, F, and I and  $\text{NO}_2$ . Preferably  $R^6$  represents a pivoyl protecting group.

[0031] In a preferred embodiment the reaction may be carried out using pivoyl chloride in dry dichloromethane in the presence of pyridine.

[0032] In step (E), the OH groups in 3- and 4-position are selectively protected with a ketal or acetal protecting group using standard conditions to yield a compound of general formula (VII):

Formula (VII)



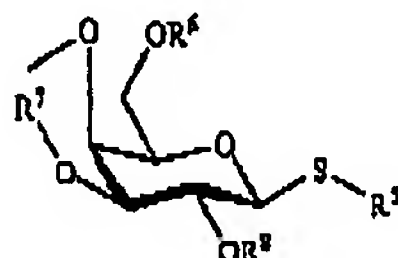
wherein  $R^5$  and  $R^6$  are as defined above; and  $R^7$  represents a ketal or acetal type protecting group selected from benzylidene, 4-nitrobenzylidene, 4-methoxybenzylidene or isopropylidene. In a preferred embodiment  $R^7$  represents an isopropylidene protecting group.

[0033] The reaction is preferably carried out in a dipolar aprotic solvent such as dimethyl formamide (DMF) or acetone in the presence of acid catalysts such as p-toluene sulfonic acid or camphorsulfonic acid using a 2,2-dialkyl-1,3-dioxane or an optionally substituted dialkylbenzylidene.

[0034] Suitable reaction temperatures range from ambient temperature to elevated temperatures. Preferably the reaction is carried out at a temperature of 25° C.

[0035] Moreover, the OH group in 2-position is protected in step (F) by reacting the compound of general formula (VII) with chloroacetyl chloride to yield a compound of general formula (VIII):

Formula (VIII)

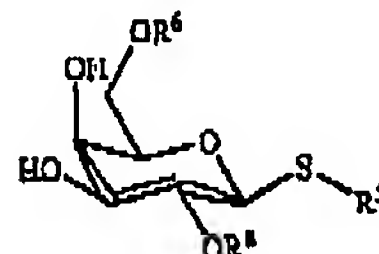


wherein  $R^5$ ,  $R^7$  and  $R^8$  are as defined above; and  $R^8$  represents a chloroacetyl protecting group.

[0036] The reaction may be carried out in a dry solvent such as dichloromethane with a base such as pyridine or triethylamine at a temperature of from 0° C. to 25° C.

[0037] In step (G) the compound of general formula (VIII) is deprotected to yield a compound of general formula (IX):

Formula (IX)

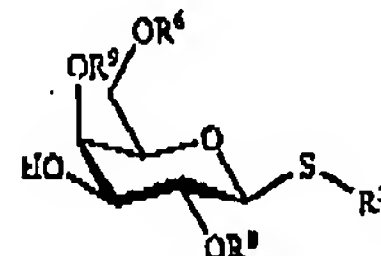


wherein  $R^5$ ,  $R^6$  and  $R^8$  are as defined above.

[0038] Deprotection may be carried out under acidic conditions by treating with aqueous acetic acid, aqueous trifluoroacetic acid or mineral or sulfonic acid.

[0039] In step (H) the compound of general formula (IX) is reacted with a trialkylorthoacetate, benzoate or pivalate, wherein the alkyl residues have 1 to 4 carbon atoms, to form an 3,4-ortho ester which is subsequently migrated to the axial 4-position under acidic conditions to yield a compound of general formula (X):

Formula (X)



wherein  $R^5$ ,  $R^6$ ,  $R^8$  are as defined above and  $R^9$  is an acetyl, benzoyl or pivoyl protecting group. In preferred embodiments  $R^9$  represent an acetate or benzoyl protecting group, which may be introduced by means of trimethyl or triethyl orthoacetate or benzoate, most preferably trimethylorthoacetate.

[0040] Step (H) may be conducted in an inert organic solvent such as acetonitrile.

[0041] Preferably the reaction is carried out in the presence of a catalyst. Any conventional catalyst used in carbohydrate chemistry may be employed. Particular preferred catalysts include p-toluenesulfonic acid, or camphor sulfonic acid. The most preferred catalyst is p-toluenesulfonic acid.

[0042] The reaction may preferably be carried out under anhydrous conditions in the presence of a water detracting means such as 4 Å mol sieves.

[0043] The free OH group in 3-position is reacted in step (I) with a protected halogen glucose derivative of general formula (XI):

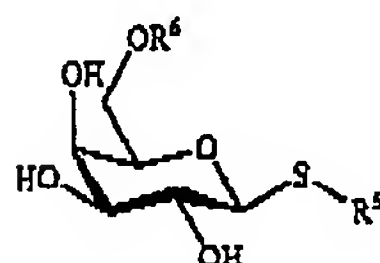
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5. The method according to claim 4, further comprising the step of:

selectively protecting the OH group in the 6-position of a compound of formula (V) as defined in claim 4 with pivoyl chloride using standard conditions to yield a compound of general formula (VI):

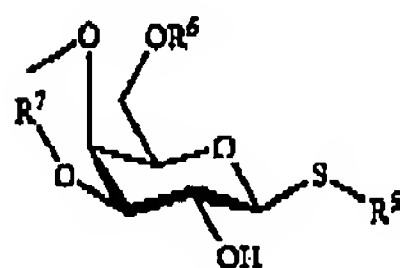


Formula (VI)

wherein  $R^5$  represents a straight or branched  $C_{1-14}$  alkyl group or a phenyl group optionally substituted with one or more  $C_{1-4}$  alkyl groups; and  $R^6$  is a pivoyl, benzoyl or substituted benzoyl protecting group, whereby the substituents are selected from alkyl groups such as methyl, halogen atoms such as Cl, Br, F, and I and  $NO_2$ .

6. The method according to claim 5, further comprising the step of:

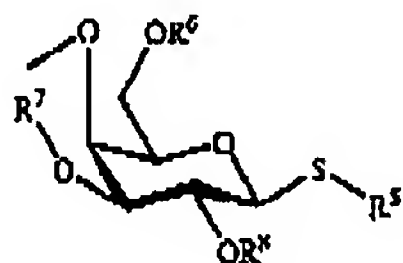
selectively protecting the OH groups in 3- and 4-position with a ketal or acetal protecting type protecting group using standard conditions, to yield a compound of general formula (VII):



Formula (VII)

wherein  $R^5$  represents a straight or branched  $C_{1-14}$  alkyl group or a phenyl group optionally substituted with one or more  $C_{1-4}$  alkyl groups and  $R^6$  is a pivoyl, benzoyl or substituted benzoyl protecting group, whereby the substituents are selected from alkyl groups such as methyl, halogen atoms such as Cl, Br, F, and I and  $NO_2$ ; and  $R^7$  represents a ketal or acetal type protecting group selected from the group consisting of benzylidene, 4-nitrobenzylidene, 4-methoxybenzylidene and isopropylidene.

7. The method according to claim 6, further comprising the step of: protecting the OH group in 2-position of the compound of general formula (VII) as defined in claim 6 with chloroacetyl chloride using standard conditions, to yield a compound of general formula (VIII):

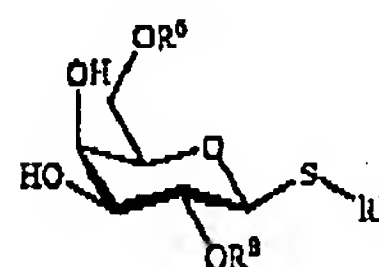


Formula (VIII)

wherein  $R^5$  represents a straight or branched  $C_{1-14}$  alkyl group or a phenyl group optionally substituted with one or

more  $C_{1-4}$  alkyl groups;  $R^6$  is a pivoyl, benzoyl or substituted benzoyl protecting group, whereby the substituents are selected from alkyl groups such as methyl, halogen atoms such as Cl, Br, F, and I and  $NO_2$ ; and  $R^7$  represents a ketal or acetal type protecting group selected from the group consisting of benzylidene, 4-nitrobenzylidene, 4-methoxybenzylidene and isopropylidene; and  $R^8$  represents a chloroacetyl protecting group.

8. The method according to claim 7, further comprising the step of: selectively deprotecting the OH group in 3- and 4-position of the compound of general formula (VIII) as defined in claim 7 using standard conditions, to yield a compound of general formula (IX):

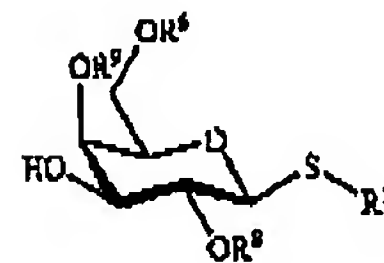


Formula (IX)

wherein  $R^5$  represents a straight or branched  $C_{1-14}$  alkyl group or a phenyl group optionally substituted with one or more  $C_{1-4}$  alkyl groups;  $R^6$  is a pivoyl, benzoyl or substituted benzoyl protecting group, whereby the substituents are selected from alkyl groups such as methyl, halogen atoms such as Cl, Br, F, and I and  $NO_2$ ; and  $R^8$  represents a chloroacetyl protecting group.

9. The method according to claim 8, further comprising the step of:

reacting the compound of general formula (IX) with a trialkylorthoacetate, benzoate or pivalate to form an 3,4-ortho ester which is subsequently migrated to the axial 4-position under acidic conditions to yield a compound of general formula (X):



Formula (X)

wherein  $R^5$  represents a straight or branched  $C_{1-14}$  alkyl group or a phenyl group optionally substituted with one or more  $C_{1-4}$  alkyl groups;  $R^6$  is a pivoyl, benzoyl or substituted benzoyl protecting group, whereby the substituents are selected from alkyl groups such as methyl, halogen atoms such as Cl, Br, F, and I and  $NO_2$ ;  $R^8$  represents a chloroacetyl protecting group; and  $R^9$  represents a benzoyl, acetyl or pivoyl protecting group.

10. The method according to claim 9, further comprising the step of: reacting the OH group in 3-position of the compound of general formula (X) as defined in claim 9 with a protected halogen glucose derivative of general formula (XI):

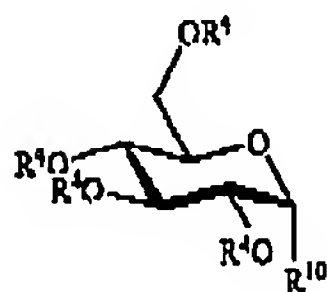


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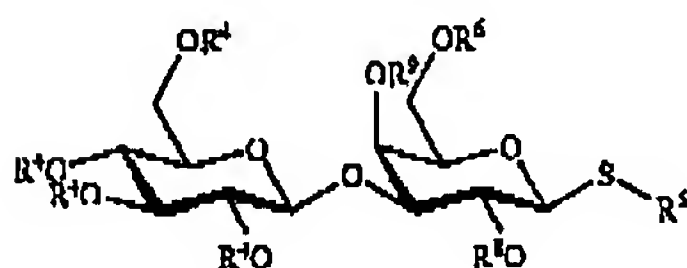
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Formula (XI)



wherein  $R^4$  independently represents a benzoyl, acetyl or pivoyl protecting group; and  $R^{10}$  represents a halogen atom, a trichloroacetimidate group, or a thioalkyl group having 1 to 14 carbon atoms, to yield a compound of general formula (XI):

Formula (XII)



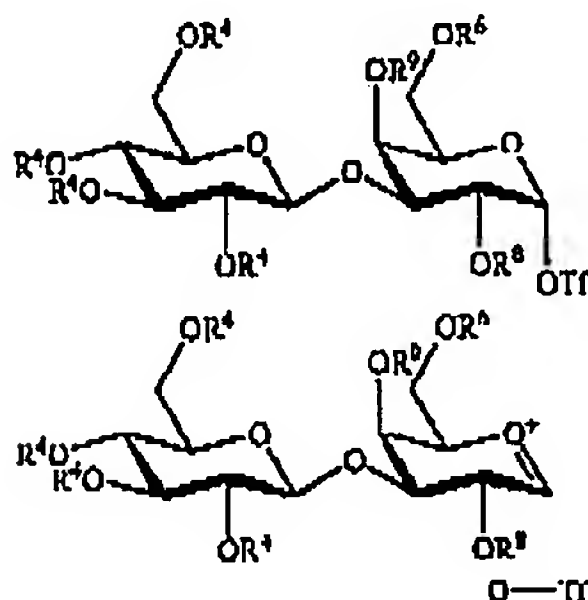
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wherein  $R^4$  independently represents a benzoyl, acetyl or pivoyl protecting group;  $R^5$  represents a straight or branched  $C_{1-4}$  alkyl group or a phenyl group optionally substituted with one or more  $C_{1-4}$  alkyl groups;  $R^6$  is a pivoyl, benzoyl or substituted benzoyl protecting group, whereby the substituents are selected from alkyl groups such as methyl, halogen atoms such as Cl, Br, F, and I and  $NO_2$ ;  $R^8$  represents a chloroacetyl protecting group; and  $R^9$  represents a benzoyl, acetyl or pivoyl protecting group.

11. The method according to claim 10, further comprising the step of:

activating the compound of general formula (XII) as defined in claim 10 by oxidizing the thio ether group to a sulfoxide using hydrogen peroxide, and subsequently treating the resulting intermediate with triflic anhydride, to yield a compound of general formula (XIII)

Formula (XIII)



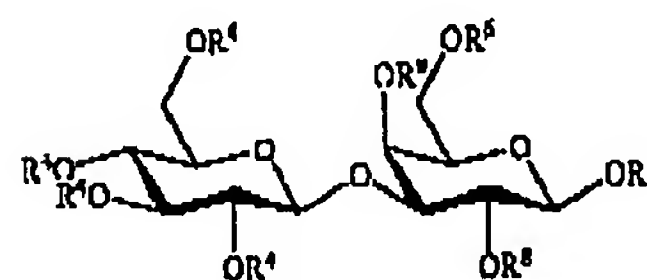
wherein each  $R^4$  independently represents a benzoyl, acetyl or pivoyl protecting group;  $R^6$  represents a pivoyl protecting group;  $R^8$  represents a chloroacetyl

protecting group;  $R^9$  represents a benzoyl, acetyl or pivoyl protecting group; and Tf represents a triflate leaving group.

12. The method according to claim 13, further comprising the step of:

selectively deprotecting the OH group in the 2-position of the compound of general formula (XV)

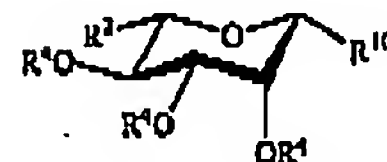
Formula (XV)



wherein  $R^1$  represents a steroid or a derivative thereof having a hydroxyl group in 3-position and no further unprotected hydroxyl groups;  $R^6$  represents a pivoyl protecting group;  $R^8$  represents a chloroacetyl protecting group and  $R^9$  represents a benzoyl, acetyl or pivoyl protecting group;

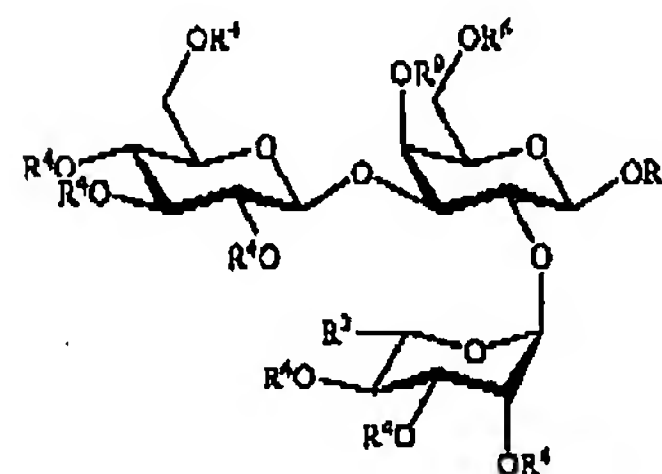
using this urea in the presence of a sterically hindered non-nucleophilic base, and subsequently reacting the resulting intermediate with a protected halogen rhamnose derivative of general formula (XVI):

Formula (XVI)



wherein  $R^2$  represents a straight or branched  $C_{1-4}$  alkyl group or a hydroxyl group;  $R^4$  independently represents a benzoyl, acetyl or pivoyl protecting group; and  $R^{10}$  represents a halogen atom, a trichloroacetimidate group, or a thioalkyl group having 1 to 14 carbon atoms; to yield a compound of general formula (XVII):

Formula (XVII)



wherein  $R^1$ ,  $R^2$ ,  $R^4$ ,  $R^6$ , and  $R^9$  are as defined above.

13. The method according to claim 12, further comprising the step of: deprotecting the compound of general formula (XVII) as defined in claim 12, to yield the compound of general formula (I)

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ATTACHMENT B

Indication of Location in the Specification As Filed  
Of Relevant Text Corresponding to Errors

Page 3, line 7

"...reacting a compound of general formula (XIII):"

Page 5, line 5

"...C<sub>1-4</sub> alkyl groups, halogen..."

Page 11, line 13

"...preferred catalyst is p-toluenesulfonic acid."

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**ATTACHMENT C**  
**Indication of Location in the Preliminary Amendment As Filed**  
**Of Relevant Text Corresponding to Errors**

Page 6, Claim 7

"...R<sup>6</sup> is a pivoly, benzoyl or substituted benzoyl protecting group, whereby the substituents..."

Page 7, Claim 8

"...wherein R<sup>5</sup> represents a straight or branched C<sub>1-14</sub> alkyl group..."

Page 7, Claim 9

"...wherein R<sup>5</sup> represents a straight or branched C<sub>1-14</sub> alkyl group..."

Page 8, Claim 10

"...R<sup>5</sup> represents a straight or branched C<sub>1-14</sub> alkyl group..."

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